PROFESSIONAL INFORMATION

VALEPTIC SYRUP has a high teratogenic potential and when used in pregnancy, may cause various major and minor congenital abnormalities of body organs and/or body structures as well as may harm the developing brain of the foetus resulting in negative effects in childhood which may include neurodevelopmental disorders such as late walking and talking, poor language skills, memory problems, lower intellectual abilities.

Exposure to VALEPTIC SYRUP in utero is also associated with an increased risk to develop autistic spectrum disorder, childhood autism and attention deficit hyperactivity disorder (ADHD). VALEPTIC SYRUP treatment should be initiated and supervised by a medical practitioner experienced in the treatment of epilepsy or bipolar disorder and VALEPTIC SYRUP should not be prescribed if the relevant Risk Minimisation Measures/Pregnancy Prevention Programme, cannot be implemented and supervised and patients are not committed to adhere to these measures.

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

VALEPTIC SYRUP 200 mg/5 mL sodium valproate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL syrup contains 200 mg sodium valproate.

Contains sugar: sorbitol (800 mg/5 mL)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Syrup

VALEPTIC SYRUP is a clear, red, syrup with a cherry caramel odour. It is free from visible matter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

VALEPTIC SYRUP is indicated for the treatment of petit mal, grand mal, mixed generalised epilepsy and temporal lobe (or psychomotor) epilepsy.

4.2 Posology and method of administration

VALEPTIC SYRUP should not be diluted.

VALEPTIC SYRUP should preferably be taken with or after food.

Adults:

An initial dose should start at 600 mg/day, in two divided doses, increasing by 200 mg/day every three days to a usual range of 1 000 to 2 000 mg/day. If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day or an additional anti–epileptic medicine may be added at a low dosage.

Children weighing more than 20 kg:

An initial dosage should start at 400 mg/day irrespective of weight, in two divided doses gradually increased until control is achieved. This is usually within the range of 20 to 30 mg/kg of body mass per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per

day.

Children weighing less than 20 kg:

A dose of 20 mg/kg daily in two divided dose may be given, this may be increased to 40 mg/kg daily in severe cases, but only if it is possible to monitor the patient's plasma-valproate concentrations. If the dosage exceeds 40 mg/kg/day, the patient's clinical chemistry and haematological parameters should be monitored.

Elderly patients – elderly patients tend to have higher serum concentrations of free (unbound) valproic acid; lower daily dosages recommended.

4.3. Contraindications

VALEPTIC SYRUP is contra-indicated for use in:

- Patients who are hypersensitive to sodium valproate or any of the excipients listed in section 6.1.
- Women and girls of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.4 and 4.6).
- Patients who are pregnant. Use of VALEPTIC SYRUP in pregnancy should be avoided (see section 4.6).
- Pre-existing liver disease or family history of severe hepatic dysfunction.
- Patient with known urea cycle disorders (see section 4.4).
- Porphyria.
- Concurrent use with MAOI (see section 4.5).
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding the mitochondrial enzyme polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome, and in children under two years of age who are suspected of having a POLG-related disorder (see section 4.4).

4.4 Special warnings and precautions for use

Although there is no specific evidence of sudden recurrence of underlying symptoms following withdrawal of VALEPTIC SYRUP, discontinuation should normally only be done under the supervision of a medical practitioner in a gradual manner. This is due to the possibility of sudden alterations in plasma concentrations giving rise to a recurrence of symptoms. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Severe liver damage:

Cases of severe liver damage, including hepatic failure sometimes resulting in fatalities have been reported.

Experience in epilepsy has indicated that patients most at risk especially in cases of multiple anticonvulsant therapy are infants and in particular young children under the age of 3 years and those with severe seizure disorders, particularly those with brain damage, mental retardation and (or) congenital metabolic or degenerative disease associated with mental retardation. After the age of 3 years, the incidence of occurrence is significantly reduced and progressively decrease with age.

The concomitant use of salicylates should be avoided in children under 3 years due to the risk of liver toxicity. Additionally, salicylates should not be used in children under 16 years (see aspirin/salicylate product information on Reye's syndrome).

Monotherapy is recommended in children under the age of 3 years when prescribing valproate, but the potential benefit of valproate should be weighed against the risk of liver damage or pancreatitis in such patients prior to initiation of therapy.

In most cases, such liver damage occurred during the first 6 months of therapy, the period of maximum risk being 2 – 12 weeks.

Suggestive signs:

Clinical symptoms are essential for early diagnosis. In particular the following conditions, which may precede jaundice, should be taken into consideration especially in patients at risk (see above "Conditions of occurrence"):

- Non-specific symptoms, usually of sudden onset, such asthenia, malaise, anorexia, lethargy, oedema and drowsiness, which are sometimes associated with repeated vomiting and abdominal pain.
- In patients with epilepsy, recurrence of seizures**.**

These are an indication for immediate withdrawal of the drug.

Patients (or the family of children) should be instructed to report immediately any such signs to medical practitioner should they occur. Investigations including clinical examination and biological assessment of the liver function should be undertaken immediately.

Detection:

Liver function should be performed before and then periodically monitored during the first 6 months of therapy, especially in those who seem most at risk, and those with a prior history of liver disease.

Amongst usual investigations, tests which reflect protein synthesis, particularly prothrombin rate, are most relevant.

Confirmation of an abnormally low prothrombin rate, particularly in association with other biological abnormalities (significant decrease in fibrinogen and coagulation factors, increased bilirubin level and raised transaminases) requires cessation of VALEPTIC SYRUP therapy

As a matter of precaution and in the case VALEPTIC SYRUP is taken concomitantly with salicylates, salicylates should also be discontinued since they employ the same metabolic pathway

As with most anti-epileptic drugs, increased liver enzymes are common, particularly at the beginning of therapy; they are also transient.

More extensive biological investigations (including prothrombin rate) are recommended in these patients; a

reduction in dosage may be considered when appropriate and tests should be repeated as necessary.

Pancreatitis:

Severe pancreatitis, which may result in fatalities, has been reported. Patients experiencing nausea, vomiting or acute abdominal pain should have prompt medical evaluation (including measurement of serum amylase). Young children are at particular risk. This risk is decreased with increasing age. Severe seizures, severe neurological impairment with combination anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome. In case of pancreatitis VALEPTIC SYRUP should be discontinued.

Female children, women of childbearing potential and pregnant woman:

VALEPTIC SYRUP should not be used during pregnancy and lactation

Pregnancy Prevention Programme

VALEPTIC SYRUP has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neuro-developmental disorders (see section 4.6).

VALEPTIC SYRUP is contraindicated in the following situations:

- In pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:

The medical practitioner must ensure that:

- Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the

measures needed to minimise the risks.

- The potential for pregnancy is assessed for all female patients.
- The patient has understood and acknowledged the risks of congenital malformations and neuro-developmental disorders including the magnitude of these risks for children exposed to VALEPTIC SYRUP *in utero*.
- The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception, without interruption during the entire duration of treatment with VALEPTIC SYRUP.
- The patient understands the need for regular (at least annual) review of treatment by a medical practitioner experienced in the management of epilepsy.
- The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- The patient understands the need to urgently consult her physician in case of pregnancy.
- The patient has received the Patient Guide.
- The patient has acknowledged that she has understood the hazards and necessary precautions associated with VALEPTIC SYRUP use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the medical practitioner considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

- The medical practitioner must ensure that parents/caregivers of female children understand the need to

contact the medical practitioner once the female child using VALEPTIC SYRUP experiences menarche (see section 4.3).

- The medical practitioner must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for infants exposed to VALEPTIC SYRUP in utero (see section 4.3).
- In patients who experienced menarche, the medical practitioner must reassess the need for VALEPTIC SYRUP therapy annually and consider alternative treatment options. If VALEPTIC SYRUP is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme must be discussed. Every effort should be made by the medical practitioner to switch female children on VALEPTIC SYRUP to alternative treatment before they reach adulthood (see section 4.3).

Pregnancy test

Pregnancy must be excluded before start of treatment with VALEPTIC SYRUP. Treatment with VALEPTIC SYRUP must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

Contraception

Women of childbearing potential who are prescribed VALEPTIC SYRUP must use effective contraception without interruption during the entire duration of treatment with VALEPTIC SYRUP. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of

contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception (see section 4.3).

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased VALEPTIC SYRUP efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control) when initiating or discontinuing oestrogen-containing products.

On the opposite, VALEPTIC SYRUP does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a medical practitioner

The medical practitioner should at least annually review whether VALEPTIC SYRUP is the most suitable treatment for the patient. The medical practitioner should discuss the annual risk acknowledgement form, at initiation and during each annual review, and ensure that the patient has understood its content.

Pregnancy planning

If a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess VALEPTIC SYRUP therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.6).

If switching is not possible, the woman should receive further counselling regarding the risks of valproate

for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using VALEPTIC SYRUP becomes pregnant, she must be immediately referred to a medical practitioner to re-evaluate treatment with VALEPTIC SYRUP and consider alternative treatment options. The patients with VALEPTIC SYRUP-exposed pregnancy and their partners should be referred to a medical practitioner experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists or healthcare professionals must ensure that

- the patient card is provided with every VALEPTIC SYRUP dispensing and that the patients understand its content
- patients are advised not to stop their VALEPTIC SYRUP medication and to immediately contact a medical practitioner in case of planned or suspected pregnancy.

Educational materials:

In order to assist healthcare professionals and patients in avoiding exposure to VALEPTIC SYRUP during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of VALEPTIC SYRUP in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using VALEPTIC SYRUP.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of VALEPTIC SYRUP treatment by the medical practitioner.

Aggravated convulsions:

As with other anti-epileptic drugs, some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with VALEPTIC SYRUP. In case of aggravated convulsions, the patients should be advised to consult their physician immediately (see section 4.8).

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with VALEPTIC SYRUP in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data does not exclude the possibility of an increased risk for VALEPTIC SYRUP.

Patients should be monitored for signs of suicidal ideation and behaviour, and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice immediately should signs of suicidal ideation or behaviour emerge.

Carbapenem medicine:

The concomitant use of VALEPTIC SYRUP and carbapenem medicines is not recommended (see section 4.5)

Patients with known or suspected mitochondrial disease:

VALEPTIC SYRUP may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear encoded POLG gene. In particular, VALEPTIC SYRUP-induced acute liver failure and liver-related deaths have been reported at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for the mitochondrial enzyme

polymerase γ (POLG), e.g. Alpers-Huttenlocher Syndrome.

POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to unexplained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, ophthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders (see section 4.3).

Haematological tests:

Blood test (blood cell count, including platelet count, bleeding time and coagulation test) are recommended prior initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding (see section 4.8

Renal insufficiency

Metabolites may accumulate; valproate binding serum albumin is decreased and volume of distribution is increased

In patients with renal insufficiency, it may be necessary to decrease dosage. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see section 4.2 and 5.2).

Patients with systemic lupus erythematosus:

Although immune disorders have been infrequently noted during the use of VALEPTIC SYRUP, the potential benefit of VALEPTIC SYRUP should be weighed against the risk in patients with systemic lupus erythematosus (see section 4.8).

Urea cycle disorders:

VALEPTIC SYRUP may cause hyperammonaemia.

When a urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with VALEPTIC SYRUP (see section 4.3).

Weight gain:

VALEPTIC SYRUP very commonly causes weight gain, which may be marked and progressive. Patients should be warned of the risk of weight gain at the initiation of therapy; and appropriate strategies should be adopted to minimise it (see section 4.8).

Diabetic patients:

VALEPTIC SYRUP is eliminated mainly through the kidney, partly in the form of ketone bodies, and this may give false positive readings in the urine testing of possible diabetics.

Dental

Prolonged bleeding time and/or haemorrhaging; leucopenia and thrombocytopenia may result in increased incidence of microbial infection, delayed healing and gingival bleeding.

Surgical

Prolonged bleeding time and/or haemorrhaging; leucopenia and thrombocytopenia may cause surgical complications.

Carnitine palmitoyltransferase (CPT) type II deficiency:

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the

greater risk of rhabdomyolysis when taking VALEPTIC SYRUP.

Alcohol use during treatment with VALEPTIC SYRUP:

Alcohol intake is not recommended during treatment with VALEPTIC SYRUP.

Adult males intending procreation:

VALEPTIC SYRUP has been associated with male fertility dysfunction that may not always be reversible after treatment discontinuation (see section 4.6 and 4.8). The medical practitioner should discuss with adult males their intent to procreate, when prescribing VALEPTIC SYRUP. If procreation is intended, valproate should be used only if alternative treatment options are not suitable.

VALEPTIC SYRUP contains sorbitol

VALEPTIC SYRUP contains 800 mg sorbitol in each 5 mL dose.

Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may also cause gastrointestinal discomfort and mild laxative effect, as well as affecting the bioavailability of other medicinal products for oral use administered concomitantly.

VALEPTIC SYRUP contains sodium

VALEPTIC SYRUP contains less than 1 mmol sodium (23 mg) per 5 mL, that is to say essentially ‘sodium-free’.

VALEPTIC SYRUP contains sodium methylparaben and sodium propylparaben:

May cause allergic reactions (possibly delayed).

Paediatric population

Children are at an increased risk of developing serious or fatal hepatotoxicity.

Liver dysfunction, including hepatic failure resulting in fatalities has occurred in patients taking VALEPTIC SYRUP. Patients at greatest risk are children taking other anticonvulsants together with VALEPTIC SYRUP.

Some psychiatric disorders, including aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder, may be observed in paediatric patients receiving VALEPTIC SYRUP (see section 4.8). Current evidence is inconclusive as to the possibility of harm to reproductive organs, skeletal system growth or developing brain of patients less than 18 years of age.

In male children less than 18 years of age, VALEPTIC SYRUP should be used with caution and in alignment with guidelines on the use of antiepileptics.

VALEPTIC SYRUP can be used in female children less than 18 years of age only if there is no suitable safer alternative therapy or alternate therapy have failed to control the epilepsy. In addition, for female children, ensure that the conditions of the pregnancy prevention programme are met (see section 4.4 and 4.6).

4.5 Interaction with other medicines and other forms of interaction

VALEPTIC SYRUP may interact with other medicines or other medicines may interact with VALEPTIC SYRUP**.**

Effects of VALEPTIC SYRUP on other medicines:

- **VALEPTIC SYRUP** should not be used with monoamine oxidase inhibitors; barbiturates; lithium;

olanzapine; phenobarbital; primidone; phenytoin; carbamazepine; lamotrigine; felbamate; rufinamide; propofol; zidovudine; nimodipine; temozolomide, and possibly other hydantoin anticonvulsants; clonazepam and anticoagulants and other products which have anticoagulant properties (e.g. warfarin and salicylates).

Neuroleptics/Antipsychotics, MAO inhibitors, antidepressants and benzodiazepines

VALEPTIC SYRUP may potentiate the effect of other psychotropics such as neuroleptics/antipsychotics, MAO inhibitors, antidepressants and benzodiazepines; therefore, clinical monitoring is advised and dosage of other psychotropics should be adjusted when appropriate.

In particular, a clinical study has suggested that adding olanzapine to VALEPTIC SYRUP or lithium therapy may significantly increase the risk of certain adverse events associated with olanzapine e.g. neutropenia, tremor, dry mouth, increased appetite and weight gain, speech disorder and somnolence.

Lithium

VALEPTIC SYRUP has no effect on serum lithium levels.

Olanzapine

VALEPTIC SYRUP may decrease the olanzapine plasma concentration.

Phenobarbital

VALEPTIC SYRUP may increase phenobarbital plasma concentrations as a result of inhibition of hepatic catabolism and sedation may occur, particularly in children. Throughout the first 15 days of combined treatment, clinical monitoring is recommended with immediate reduction of phenobarbital doses if sedation occurs and determination of phenobarbital plasma levels when appropriate.

Primidone

VALEPTIC SYRUP may increase primidone plasma levels with exacerbation of its adverse effects, including sedation. These signs may cease with long term usage. Clinical monitoring is therefore recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Phenytoin

VALEPTIC SYRUP may decrease phenytoin total plasma concentration.

VALEPTIC SYRUP may increase phenytoin free form resulting in possible overdosage symptoms, due to displacing phenytoin from its plasma protein binding sites and reducing its hepatic catabolism. Clinical monitoring is recommended. Once phenytoin plasma levels are determined the free form should be re-evaluated.

Carbamazepine

Clinical toxicity may occur when VALEPTIC SYRUP is administered concurrently with carbamazepine. The toxic effect of carbamazepine may be enhanced. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.

Lamotrigine

VALEPTIC SYRUP may reduce lamotrigine metabolism and increase its mean half-life by nearly two-fold. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Therefore, clinical monitoring is recommended and appropriate dosage adjustment may be required when lamotrigine dosage is decreased. The risk of rash may be increased by co-administration of lamotrigine with VALEPTIC SYRUP**.**

Felbamate

VALEPTIC SYRUP may decrease the felbamate mean clearance by up to 16 %.

Rufinamide

VALEPTIC SYRUP may lead to an increase in plasma levels of rufinamide. This increase is dependent on concentration of valproic acid. Caution should be exercised, in particular in children, as this effect is larger in this population.

Propofol

VALEPTIC SYRUP may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.

Zidovudine

Increased zidovudine toxicity may occur since VALEPTIC SYRUP may raise zidovudine plasma concentration.

Nimodipine

In patients concomitantly treated with VALEPTIC SYRUP and nimodipine the exposure to nimodipine can be increased by 50 %. The nimodipine dose should therefore be decreased in case of hypotension.

Temozolomide

Co-administration of temozolomide and VALEPTIC SYRUP may cause a small decrease in the clearance of temozolomide that is not thought to be clinically relevant.

Effects of other medicines on VALEPTIC SYRUP:

Anti-epileptics

Antidepressants and neuroleptics may antagonise the anti- epileptic activity of VALEPTIC SYRUP thus may lower the seizure threshold. This may necessitate VALEPTIC SYRUP dosage adjustments. Anti-epileptics with enzyme inducing effects (including phenytoin, phenobarbital and carbamazepine) may decrease valproate serum concentrations. In the case of combined therapy dosages should be adjusted according to blood levels.

VALEPTIC SYRUP metabolite levels may be increased in the case of concomitant use with phenytoin or phenobarbital. Therefore, patients treated with those two drugs should be carefully monitored for signs and symptoms of hyperammonaemia.

On the other hand, combination of felbamate and VALEPTIC SYRUP decrease valproic acid clearance by 22 – 50 % and consequently increase the valproic acid plasma concentrations. Dosages of VALEPTIC SYRUP should thus be monitored.

Anti-malarial medicines

Mefloquine and chloroquine increases valproic acid metabolism and may lower the seizure threshold; therefore, epileptic seizures may occur in cases of combined therapy. Accordingly, the dosage of VALEPTIC SYRUP may need adjustment.

Highly protein bound medicines

Valproate free serum levels may be increased with the concomitant use of VALEPTIC SYRUP and highly protein bound medicines such as aspirin**.** The anticoagulant effect of vitamin K dependent factor may thus also be increased**.**

Vitamin K-dependent factor anticoagulants

The anticoagulant effect of medicines such as warfarin and other coumarin anticoagulants may be increased due to its displacement from plasma protein binding sites by VALEPTIC SYRUP. Therefore, a close monitoring of international normalisation ratio (INR) or prothrombin time should be performed.

Cimetidine or erythromycin

Serum valproate levels may be increased due to a reduced hepatic metabolism when used concurrently with cimetidine or erythromycin.

Carbapenem antibiotics (such as panipenem, imipenem and meropenem)

Carbapenem antibiotics such as imipenem, meropenem and ertapenem may cause a decrease in valproate blood levels, resulting in a 60 – 100 % decrease in valproic acid levels within two days, leading to convulsions when combined. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem medicines in patients stabilised on valproic acid should be avoided (see section 4.4). If these antibiotics have to be administered, the close monitoring of valproate blood levels is recommended.

Rifampicin

Rifampicin may decrease the valproic acid blood levels resulting in a lack of therapeutic effect. Therefore, VALEPTIC SYRUP dosage adjustment may be necessary when it is co-administered with rifampicin.

Protease inhibitors

Protease inhibitors such as lopinavir and ritonavir decrease VALEPTIC SYRUP plasma level when co-administered.

Cholestyramine

Cholestyramine may lead to a decrease in plasma level of VALEPTIC SYRUP when co-administered.

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives

Oestrogens are inducers of the UDP-glucuronosyl transferase (UGT) isoforms involved in valproate glucuronidation and may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased valproate efficacy (see section 4.4). Consider monitoring of VALEPTIC SYRUP serum levels.

VALEPTIC SYRUP usually has no enzyme inducing effect; thus VALEPTIC SYRUP does not reduce the efficacy of oestrogen- and/or progestogen-containing medicines in women receiving hormonal contraception.

Other interactions:

Caution is advised when using VALEPTIC SYRUP in combination with newer anti-epileptics whose pharmacodynamics may not be well established.

Concomitant administration of VALEPTIC SYRUP and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. In patients taking these two drugs, careful monitoring of signs and symptoms is advised in particularly at-risk patients such as those with pre-existing encephalopathy.

Quetiapine

Co-administration of VALEPTIC SYRUP and quetiapine may increase the risk of neutropenia/leucopenia.

4.6 Fertility, pregnancy and lactation

VALEPTIC SYRUP is contraindicated during pregnancy and lactation (see section 4.3)

Woman of childbearing potential

VALEPTIC SYRUP is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

Oestrogen-containing products

Oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may increase the clearance of valproate, which would result in decreased serum concentration of valproate and potentially decreased VALEPTIC SYRUP efficacy (see section 4.4 and 4.5).

Pregnancy

VALEPTIC SYRUP is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.

VALEPTIC SYRUP crosses placenta and may cause neural tube defects (anencephaly, meningomyelocele and spina bifida) in the foetus. Haemorrhagic syndrome may occur in the neonate if VALEPTIC SYRUP is taken by pregnant women.

Pregnancy exposure risk related to VALEPTIC SYRUP

Both VALEPTIC SYRUP monotherapy and VALEPTIC SYRUP polytherapy including other anti-epileptics are frequently associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including VALEPTIC SYRUP may be associated with a greater risk of congenital malformations than VALEPTIC SYRUP monotherapy.

VALEPTIC SYRUP was shown to cross the placental barrier both in animal species and in humans (see

section 5.2).

In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

Congenital malformations

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73 % of children of epileptic women exposed to VALEPTIC SYRUP monotherapy during pregnancy suffer from congenital malformations (95 % CI: 8.16 – 13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2 – 3 %. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

In utero exposure to VALEPTIC SYRUP may also result in hearing impairment or deafness due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function. Cases describe both unilateral and bilateral deafness or hearing impairment. Outcomes were not reported for all cases. When outcomes were reported, the majority of the cases did not recover.

Developmental disorders

Data have shown that exposure to VALEPTIC SYRUP in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool children exposed in utero to valproate show that up to 30 – 40 % experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of VALEPTIC SYRUP exposure in utero was on average 7 – 10 points lower than those children exposed to other anti-epileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to VALEPTIC SYRUP that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long-term outcomes.

Available data from a population-based study show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately 3-fold) and childhood autism (approximately 5-fold) compared to the unexposed population in the study.

Available data from another population-based study show that children exposed to VALEPTIC SYRUP in utero are at increased risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study.

If a woman plans a pregnancy

If a woman is planning to become pregnant, a medical practitioner experienced in the management of epilepsy must reassess VALEPTIC SYRUP therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued (see section 4.4). If switching is not possible, the woman should receive further counselling regarding the risks of VALEPTIC SYRUP for the unborn child to support her informed decision-making regarding family planning.

Pregnant women

VALEPTIC SYRUP as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4). If a woman using valproate becomes pregnant, she must be immediately referred to a medical practitioner to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of VALEPTIC SYRUP in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive VALEPTIC SYRUP for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose VALEPTIC SYRUP into several small doses to be taken throughout the day.
- The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All patients with VALEPTIC SYRUP-exposed pregnancy and their partners should be referred to a medical practitioner experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies.

However, the available evidence does not suggest it prevents the birth defects or malformations due to VALEPTIC SYRUP exposure.

Risks associated with epilepsy:

Notwithstanding those potential risks, no sudden discontinuation in the anti-epileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both the mother and the foetus.

Risk in the neonate:

Cases of haemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken VALEPTIC SYRUP during pregnancy. This haemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenaemia and/or to a decrease in other coagulation factors. Afibrinogenaemia has also been reported and may be fatal. Hypofibrinogenaemia can be related to a decrease in coagulation factors. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.

Cases of hypoglycaemia have been reported in neonates whose mothers have taken VALEPTIC SYRUP during the third trimester of their pregnancy.

Cases of hypothyroidism have been reported in neonates whose mothers have taken VALEPTIC SYRUP during pregnancy.

Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken VALEPTIC SYRUP during the last trimester of their pregnancy.

Breastfeeding

VALEPTIC SYRUP is excreted in human breast milk with a concentration ranging from 1 – 10 % of maternal serum levels and should be avoided during breastfeeding. Haematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

Fertility

Amenorrhoea, menstrual disorders, polycystic ovaries, increased testosterone levels and impairment of ovarian function and or fertility have been reported in women using VALEPTIC SYRUP (see section 4.8).

VALEPTIC SYRUP administration may also impair fertility in men (see section 4.8).

Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

Very low concentrations of valproate have been detected in semen of males on treatment with VALEPTIC SYRUP.

It is not known with certainly if fertility would be affected by VALEPTIC SYRUP treatment in children less than 18 years of age, as valproate may interact with sex hormones.

4.7 Effects on the ability to drive and use machines

Patients should be warned of the risk of transient drowsiness, especially in cases of anti-convulsant polytherapy or association with benzodiazepines (see section 4.5); caution when driving or doing activities requiring alertness.

Avoid use of alcoholic beverages or other CNS depressants during therapy.

4.8 Undesirable effects

System organ class	**Frequent**	**Less frequent**	**Frequency not known**
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Myelodysplastic syndrome	
Blood and lymphatic system disorders	Anaemia, thrombocytopenia, (see section 4.4)	Bruising, red cell hypoplasia, pancytopenia, leucopenia, bone	

		marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis.	
The blood picture returned to normal when the drug was discontinued.			
Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (VALEPTIC SYRUP has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see section 4.6).			
Endocrine disorders		Hyperglycaemia, syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase), hypothyroidism (see section 4.6).	
Metabolism and nutrition disorders	Hyponatraemia, weight increased*,	hyperammonaemia* (see section 4.4),	

	encephalopathy in patients with urea cycle disorders,	obesity.	
*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).			
*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur VALEPTIC SYRUP should be discontinued. Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2). In such cases further investigations should be considered.			
Psychiatric disorders	Confusion, hallucinations, occasionally aggression, agitation, disturbance in attention, hyperactivity, behavioural deterioration, amnesia and suicidal ideation.	Behavioural, mood or mental changes, emotional lability, depression, drowsiness, thinking abnormalities, unusual excitement, restlessness, irritability, abnormal behaviour, psychomotor hyperactivity, learning disorder.	
Nervous system disorders	Convulsion*, headache, insomnia, nervousness, nystagmus, memory	Loss of seizure control, increasing clouding of consciousness, tremor,	

	impairment, somnolence, tremor, extrapyramidal disorder, stupor*.	sedation, coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4), reversible dementia associated with reversible cerebral atrophy, cognitive disorder.	
Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.			
*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.			
An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.			
Eye disorder	Amblyopia	Diplopia, conjunctivitis, dry	

		eyes, painful eyes.	
Ear and Labyrinth disorders	Tinnitus, deafness, a cause and effect relationship has not been established.	Otitis media, vertigo, ear disorders or pain.	
Cardiac disorders		Palpitations.	
Vascular disorders	Haemorrhage (see section 4.4 and 4.6).	Oedema, postural hypotension, dizziness, hypertension, vasculitis.	
Respiratory, thoracic and mediastinal disorders	Dyspnoea, flu–like symptoms, pharyngitis.	Pneumonia, bronchitis, epitaxis, rhinitis, sinusitis, increased cough, pleural effusion.	
Gastrointestinal disorders	Vomiting; acute abdominal pain, minor gastric irritation and nausea, diarrhoea, indigestion, dyspepsia, stomatitis, gastralgia, gingival disorder (mainly gingival hyperplasia).	Haematemesis, periodontal abscess, anorexia or increase in appetite, constipation, dry mouth, faecal incontinence, flatulence, gastroenteritis, glossitis, taste perversion,	

		pancreatitis, sometimes lethal (see section 4.4).	
The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking VALEPTIC SYRUP with or after food.			
Hepato-biliary disorders	Liver injury (see section 4.4)	Liver dysfunction, hepatic failure, serious or fatal hepatotoxicity, jaundice and hyperammonaemia, fulminant hepatitis.	
Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.4). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4).			
Skin and subcutaneous tissue disorders	Hypersensitivity, transient and or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.	Dry skin, ecchymosis, furunculosis, petechial pruritus, hirsutism, angioedema, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth, toxic epidermal necrolysis, Stevens -	

		Johnson syndrome, erythema multiforme, rash, drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome.	
Musculoskeletal, connective tissue and bone disorders	Trembling of hands and arms, back pain.	Leg cramps, malaise, neck pain, neck rigidity, arthralgia, arthrosis, hypertonia, myalgia, myasthenia, bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with VALEPTIC SYRUP. The mechanism by which VALEPTIC SYRUP affects bone metabolism has not been identified, systemic lupus	

		erythematosus, rhabdomyolysis (see section 4.4).	
Renal and urinary disorders	Urinary incontinence.	Renal failure, enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with VALEPTIC SYRUP therapy, but the mode of action is as yet unclear.	
Reproductive system and breast disorders	Irregular periods, dysmenorrhea.	Vaginitis, vaginal haemorrhage, amenorrhoea and gynaecomastia, male infertility, polycystic ovaries, impairment of	

		ovarian function and of fertility in females.	
Congenital, familial and genetic disorders	Teratogenicity (see section 4.4 and 4.6)		
General disorders and administration site conditions		Hypothermia, non-severe peripheral oedema	
Investigations		Coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)	Reduction of fibrinogen.

Paediatric population

The safety profile of VALEPTIC SYRUP in the paediatric population is comparable to adults, but some ADRs are more severe or principally observed in the paediatric population. There is a particular risk of severe liver damage in infants and young children especially under the age of 3 years. Young children are

also at particular risk of pancreatitis. These risks decrease with increasing age (see section 4.4). Psychiatric disorders such as aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder are principally observed in the paediatric population. Based on a limited number of post-marketing cases, Fanconi Syndrome, enuresis and gingival hyperplasia have been reported more frequently in paediatric patients than in adult patients.

Neurodevelopmental problems such as late walking and talking, poor language skills, memory problems, lower intellectual abilities, autistic syndrome and ADHD have been observed in children exposed in utero (see section 4.6).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

Symptoms

Cases of accidental and deliberate VALEPTIC SYRUP overdose have been reported. At plasma concentrations of up to 5 – 6 times the maximum therapeutic levels, there are unlikely to be any symptoms other than nausea, vomiting and dizziness.

Clinical signs of acute massive overdose, i.e. plasma concentration 10 – 20 times maximum therapeutic levels, usually include CNS depression or coma, with muscular hypotonia, hyporeflexia, miosis, impaired respiratory function, metabolic acidosis, hypotension and circulatory collapse/shock. A favourable outcome

is usual; however, some deaths have occurred following massive overdose.

The symptoms of overdosage may vary and can include seizures when plasma concentrations are high (see also section 5.2). Cases of intracranial hypertension related to cerebral oedema have been reported.

The presence of sodium content in the VALEPTIC SYRUP formulations may lead to hypernatraemia when taken in overdose.

Death may result from overdosage.

Treatment

Hospital management of overdose should be symptomatic, including cardio-respiratory monitoring. Gastric lavage may be useful up to 10 to 12 hours after ingestion.

Haemodialysis and haemoperfusion have been used successfully.

Naloxone has been successfully used in a few isolated cases, sometimes in association with activated charcoal given orally.

In case of massive overdose, haemodialysis and haemoperfusion have been used successfully.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Anti-epileptics; Fatty acid derivatives

ATC code: N03AG01

Valproate is an antiepileptic which produces a direct or secondary increase in concentrations of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), possibly caused by its decreased metabolism or decreased reuptake in brain tissues.

5.2 Pharmacokinetic properties

Valproic acid is absorbed rapidly and completely after oral administration. Peak concentration in plasma is observed in 1 to 4 hours, although this can be delayed for several hours if ingested with meals. The binding to plasma protein is about 90 %. The vast majority of valproate (95 %) undergoes hepatic metabolism, with less than 5 % excreted unchanged in urine. The half-life of valproate is approximately 15 hours but is reduced in patients taking other antiepileptic medicines. Valproic acid is extensively metabolised in the liver, a large part by glucuronidation and the rest by a variety of complex pathways. It does not appear to enhance its own metabolism, but metabolism may be enhanced by other medicines which induce hepatic microsomal enzymes. It is excreted in the urine almost entirely in the form of its metabolites.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium methylparaben 0,1 % (E 219)

sodium propylparaben 0,04 % (E 216)

liquid sorbitol (E 420)

hydroxyethylcellulose/natrosol (E 1525)

saccharin sodium (E 954)

citric acid monohydrate (E 330)

cherry sweet flavour 96475-33

colour carmoisine red (14720)

purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a dry place at or below 25 ºC, away from direct sunlight.

PROTECT FROM LIGHT.

6.5 Nature and contents of the container

VALEPTIC SYRUP is packed in:

- 150 ml 28 mm medical round amber PET bottle fitted with a White PP 28 mm ROPP closure with 3 PCS TE.
- 150 ml 28 mm MEDROPP generic amber glass bottle fitted with a white 28 mm EXPE Screw Generic Closure.
- 300 ml 28 mm medical round amber PET bottle fitted with a White PP 28 mm ROPP closure with 3 PCS TE.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

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Erand Gardens

Midrand

1685

Private Bag X69

Bryanston, 2093

www.adcock.co.za

8. REGISTRATION NUMBERS

43/2.5/0267

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION

Date of registration: 18 February 2016

10. DATE OF THE REVISION OF THE TEXT

06 June 2022